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| 10/542,313 | 07/15/2005 | Ronald D. Guiles | RG-2002-002 | 2672 |

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| EXAMINER | |
|---|---|
| NIEBAUER, RONALD T | |

| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/542,313 | GUILES ET AL. | |
| | Examiner | Art Unit | |
| | Ronald T. Niebauer | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24,26 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election of a compound of R1-R2-R3 of claim 24 (R1 is hexacyclen, R2 is a polyglycine moiety, R3 is beta-nicotinamide adenine dinucleotide) in the reply filed on 12/12/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-23,25,27-34 have been cancelled.

It is noted that applicant stated that they believe claims 23,35-37 read on the elected species. However, there is no claim 36-37. Further, the elected species reads on claim 26.

Claims 24,26,35 are under consideration.

The elected species (as currently interpreted, see 112 2nd below) and claims 24,26, and 35 were searched and found to be free of the prior art. However, since there are other rejections, no claim is listed as allowable.

### *Claim Objections*

Applicant is advised that should claim 24 be found allowable, claim 26 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing,

despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In the instant case, claim 24 is drawn to a compound of R1-R2-R3 where R1 is hexacyclen, R2 is a polyglycine moiety, R3 is beta-nicotinamide adenine dinucleotide. Claim 26 is drawn to a compound of R1-R2-R3 where R1 is hexacyclen, R2 is a polyglycine moiety, R3 is beta-nicotinamide adenine dinucleotide. Claim 26 includes additional language (for example, 'a moiety that binds…') however the language does not result in a structural difference (see MPEP 2112.01) so the scope of the claims is the same.

## *Specification*

The disclosure is objected to because of the following informalities:

The specification page 22 last paragraph refers to experimental conditions that were similar to experiments performed by McClendon's group and a reference is listed. However, the journal of the reference is not listed and as such the reference can not be located.

Appropriate correction is required.

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 24,26,35** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24,26 and dependent claim 35 recite that R2 is a polyglycine moiety containing between 1 and 3 glycines. The prefix poly- is typically used to refer to more than one. However, one of the possibilities is that there is one glycine which would not be a 'polyglycine'. As such, the scope of the invention is unclear.

Claim 26 recites H26, E43, E44, E48, A54, D60, H88, A88, I24, L25, H26, H27. These abbreviations have not been clearly defined in the claim. Often times H is used to represent hydrogen, however H can also be used to represent the amino acid histidine. It appears that applicant is referring to amino acids on a particular protein. However, the exact protein referred to is unclear. It appears that applicant is referring to cytochrome b5, however it is unclear which species the protein is from (human, rat, mouse, or elephant for example).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 24,26,35** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly,

> enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

*(1) The nature of the invention:*

Claims 24 and 26 are drawn to compounds. Claim 35 is drawn to a pharmaceutical composition. Although claims 24,26, and 35 do not expressly recite the use or pharmaceutical use of the compounds the title of the specification states that the compounds are for treatment of sickle cell disease. The intended use (i.e. the treatment of sickle cell disease) is also discussed in the specification (page 1 section 02, page 6 section 11 for example). In the instant case, there is no other use that would reasonably correlate with the scope of the claims (see MPEP section 2164.01(c)).

*(3) The state of the prior art and (4) the predictability or unpredictability of the art:*

Applicants discuss that numerous approaches to sickle cell disease have been employed including transfusion therapy (section 06 page 2-3), the use of hydroxyurea (section 07 page 3-4), and bone marrow transplantation (section 08 page 4). Applicants state that attempts at hemoglobin-directed antisickling agents have been unsuccessful (section 03 page 2). Applicants state that 'sickle cell disease is a serious problem for which no effective solution is available' (section 09 page 5).

In the instant application, the asserted approach to treat sickle cell disease includes using compounds that inhibit cytochrome b5's action which thereby lead to an increase in methemoglobin levels (section 11 page 6; section 41 page 9-10) which is different than the approaches cited above.

With regard to the state of the art in methemoglobin levels and effect on sickle cell disease applicants refer to the work of Beutler (section 09, page 4) but do not provide the corresponding non-patent literature. A copy of the Beutler document (Beutler, 1961, J. Clin. Invest. V40, 1856-1871) is provided (it is noted that the document referred to by applicant refers to pages 56-68, however the appropriate pages are pages 1856-1871). Beutler teach that previous work has demonstrated that complete conversion of sickle hemoglobin to the methemoglobin derivative prevented the sickling process (page 1856 column 2 first paragraph). Beutler perform experiments using sodium nitrate or PAPP (page 1859 first paragraph) which are different from the compound of the instant invention. Beutler teach that 'the presence of less than 25 percent methemoglobin in red cells apparently exerts little effect on the dissociation of oxygen from oxyhemoglobin' (page 1859 first complete paragraph). In the Figure 4 caption (and last paragraph of page 1850), Beutler state that the percentage of cells distorted seems relatively independant of the percentage of methemoglobin in the red cells. In one case study, Beutler teach that it was impossible to achieve adequate levels of methemoglobinemia (page 1865 last paragraph). Beutler teach that 'it is obvious that drug-induced methemoglobinemia falls seriously short in several respects' (page 1867 last paragraph). In conclusion (page 1869 last paragraph), Beutler state that in none of the patients was there any substantial change in clinical status during drug administration and that preliminary attempts yielded unimpressive results. Therefore, it is

highly unpredictable to treat sickle cell disease by increasing methemoglobin levels. Although the instant application is targeting a similar mechanism of action, the current application uses a different compound than described by Beutler. In the instant case the claims are drawn to a compound of R1-R2-R3 of claim 24 (R1 is hexacyclen, R2 is a polyglycine moiety, R3 is beta-nicotinamide adenine dinucleotide).

Further, Franklin et al. (British Journal of Haemoatology, 1983, v54, 579-587) discuss the state of the art regarding methemoglobin levels and effect on sickle cell disease. In particular, using an in vitro system Franklin calculate the requirements necessary to prevent in vivo sickling (abstract). Franklin teach that 60% met-Hb S would be needed to prevent in vivo sickling (abstract). Franklin conclude (page 586 2nd full paragraph) that methaemoglobin production in vivo would appear to be futile since such a large proportion of met-Hb would be needed that oxygen delivery to tissues would certainly be compromised. In relation to the instant invention, the current invention is drawn to (section 09 last sentence) increasing methemoglobin but does not discuss the levels necessary or the likely futility of such levels.

With regard to the state of the art of hexacyclen (a component of the compound of the instant invention) an article by Richman is cited (section 65, Richman 1974 JACS v96 2268-2270; applicant only refers to pages 2268-2269 although the article includes page 2270) although the article has not been provided. A copy of the article is included in the reply. Richman teach the compound hexacyclen (see figure page 2269). However there is no explicit teaching that hexacyclen would be effective at treating sickle cell disease. In fact, Richman do not teach any functional properties of the compounds.

With regard to the state of the art with beta-nicotinamide adenine dinucleotide (a component of the compound of the instant invention), Bland et al. (US 2002/0192310) teach that nicotinamide adenine dinucleotide (section 0119) is synthesized in the body and is widespread. However there is no explicit or implicit teaching that nicotinamide adenine dinucleotide would be effective at treating sickle cell disease. In fact, since the compound is already widespread in the body it does not follow that it would then be effective at treating sickle cell disease.

In the application, applicants report interaction studies between cytochrome b5 and particular compounds (example 1,2,8). It is asserted (section 41) that by binding to cytochrome b5 that the incidence of sickling is reduced. Paltauf (JBC 1974, v249 2661-2662, a copy of which is provided) is cited as an article regarding the state of the art in correlating binding or interactions with cytochrome b5. Paltauf teach that an antibody was generated that is specific to cytochrome b5 (abstract page 2661 2nd column 2nd full paragraph). Paltauf state that biosynthesis of certain compounds is inhibited by binding to cytochrome b5 (abstract). However, Paltauf does not explicitly or implicitly correlate the binding to a reduction of sickling. As such, one would not predict that binding or interaction with cytochrome b5 would necessarily correlate to treatment of sickle cell disease.

Taken together, treatments of sickle cell disease are known, however the treatments via the mechanism described in the instant application are highly unpredictable (see Beutler and Franklin). Further, the use of the compound of the instant invention is unpredictable since no data for the compound R1-R2-R3 is available related to treatment of sickle cell disease and further there is not even data related to treatment of sickle cell disease for the individual components (see Richman and Bland) of the compound. Further, as evidenced by Paltauf

correlating binding of cytochrome b5 does not necessarily lead to an expectation of the ability to treat sickle cell disease.

*(5) The relative skill of those in the art:*

The level of skill in the art is high.

*(2) The breadth of the claims*

Claims 24 and 26 are drawn to compounds. Claim 35 is drawn to a pharmaceutical composition. Although claims 24,26, and 35 do not expressly recite the use or pharmaceutical use of the compounds the title of the specification states that the compounds are for treatment of sickle cell disease. The intended use (i.e. the treatment of sickle cell disease) is also discussed in the specification (page 1 section 02, page 6 section 11 for example). In the instant case, there is no other use that would reasonably correlate with the scope of the claims (see MPEP section 2164.01(c)).

*(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:*

The examples provided by the applicant are not for the compound of the instant invention. In example 2 applicant shows that hexacyclen (not hexacyclen with polyglycine and beta-nicotinamide adenine dinucleotide as claimed) interacts with cytochrome b5. However, the strength of the interaction is not reported. It is noted that applicant asserts that the binding is with high affinity (page 10 first line), however the data is used to show interactions, not necessarily strength of interactions. Further, the data is for hexacyclen, not the compound of the claimed invention.

In example 3 applicant refers to data from ATP, not beta-nicotinamide adenine dinucleotide or the compound of the instant invention. The data implies an interaction between ATP and cytochrome b5. Applicant states that binding is distinct from the binding of hexacyclen. However, claim 26 states that hexacyclen binds to among other amino acids H26. Claim 26 also states that beta-nicotinamide adenine dinucleotide binds to among other amino acids H26. As asserted both hexacyclen and beta-nicotinamide adenine dinucleotide bind to the same site H26. If two individual components of the compound bind to the same site one of skill in the art would question if the compound as a whole would be effective. Further, even if individual components fit into particular binding sites one would not necessarily conclude that the components attached via a linker would behave in the same manner. In particular, the linker may make the compound too rigid and not allow for access to both binding sites. Further, there are steric considerations since individual components are smaller than the compound as claimed.

In example 9 functional assays using hexacyclen, not the compound of the instant invention, are performed. However, the specification page 22 last paragraph refers to experimental conditions that were similar to experiments performed by McClendon's group and a reference is listed. However, the journal of the reference is not listed and as such the reference can not be located. As such, the scope and results of example 9 can not be interpreted. Further, characterizing the experiments as 'similar' does not provide adequate description of the scope of the experiments.

Taken together, the working examples have shown possible interaction between components of the compound and cytochrome b5. However, no data for the compound of the invention has been provided. No functional data (example 9 is uninterruptible) has been

presented. In particular, it is not evident that an interaction with cytochrome b5 will necessarily inhibit the activity of cytochrome b5. Even if cytochrome b5 function is altered to some extent, it is unclear want consequences that would lead to in vitro or in vivo with regards to treating sickle cell disease. In particular one would not recognize that an adequate increase in the amount of methemoglobin would result as asserted (page 15 section 54 first sentence). Further, the asserted synergistic behavior described (section 53 last two sentences) is not evident from the examples.

It is noted that section 2164.02 of the MPEP states that working examples are factors to be considered especially for undeveloped arts. In the instant case since no successful treatments of sickle cell disease via the proposed mechanism have been reported the current invention is considered undeveloped.

*(8) The quantity of experimentation necessary*:

Experimentation and guidance is required in numerous areas particularly related to assaying the effects of the claimed compound. In particular the binding of the compound could be investigated to determine if the compound fits into the theoretical binding pocket. Further, the strength of the binding could be investigated. The functional effects, if any, particularly relating to determining if the compound is effective at inhibiting cytochrome b5 and also determining if methemoglobin levels are increased to an adequate level could be investigated.

Taken together, such experimentation and guidance is necessary because the prior art cited above teach that the state of the art is highly unpredictable. Accordingly one would be burdened with undue experimentation to determine if the compounds of the instant invention could be used to treat sickle cell disease. Considering the state of the art as discussed by the references above, particularly with regards to the high unpredictability in the art as evidenced

therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ronald T. Niebauer whose telephone number is 571-270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ronald T Niebauer/

Examiner, Art Unit 1654

/Anish Gupta/

Primary Examiner, Art Unit 1654